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EXTERNAL SPHINCTER FATIGUE AS AN ADJUNCT TO ELECTRICAL DETRUSOR STIMULATION

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ABSTRACT

Increased resistance to urinary flow during electrical bladder stimulation is caused in dogs and rhesus macaques by striated muscle contraction conveyed mainly by the pudendal nerve. Tetanic stimulation leading to fatigue of the external sphincter immediately prior to bladder stimulation alleviates the outflow obstruction in monkeys. An implantable stimulator able to deliver a tetanic stimulus to the sphincteric region and to stimulate the detrusor is described.

The demonstration of the feasibility of electrically induced voiding in paraplegic dogs (1–10) gave impetus to clinical attempts (11–16). In the experience of most investigators, however, the results have been discouraging, especially in paraplegics. Detrusor contraction evidenced by increase in intravesical pressure could be achieved and in most patients with upper motor neuron lesions it would induce triggering of reflex emptying. The resultant urinary stream was weak, however, and the emptying of the bladder was incomplete (12, 15, 16). The need for further exploration in the laboratory thus became evident, the goal being prevention of outflow obstruction associated with bladder stimulation.

MATERIALS AND METHODS

Nineteen male rhesus macaques (5 to 6 kg) and seven male mongrel dogs were studied during general anesthesia induced by barbiturates. No premedication was given and the animals were intubated and ventilated.

Stainless steel electrodes were imbedded in the detrusor substance in bipolar or quadripolar arrangement. The bladder stimulator voltage ranged from 3 to 15 v at 30 to 40 pulses per second of 4- to 5-msec duration. A separate pair of electrodes was placed in the sphincteric region, either by a retropubic or by a perineal approach. In all dogs and in 10 monkeys the stimuli were delivered by two Grass physiological stimulators. The remaining nine monkeys were stimulated by means of an implantable radiolinked stimulator. In some cases, bladder stimulation alone was given. In others, bladder stimulation directly followed tetanic stimulation of the perineal muscles.

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All monkeys studied had normal bladder innervation; in five cases bilateral pudendal neurectomy was performed during the experiment. Three dogs had normal bladder innervation. Three were subjected to pelvic nerve resection during the experiment. The remaining dog was studied 2 weeks after establishment of spastic paraplegia by means of spinal transection at L2.

In order to obtain control over the pressure variable the experimental model described by Hald et al. (17) was employed. An external water column was connected to a No. 28 or 30 French Foley bag catheter inserted through a cystostomy at the dome of the bladder. The flow through the urethra was collected in a cylinder with a pressure transducer at its bottom. By differentiation of the pressure curve, flow rates were determined and expressed in milliliters per second. Intravesical and rectal pressures were recorded in centimeters of water.

The maximal intravesical pressure generated was 60 cm of H_2O; this was allowed to decrease as the fluid ran out of the bladder. Thus, the lowest pressure was the closure pressure of the urethra. In some instances, the inflow was stopped at a pressure between 25 and 30 cm of H_2O. At this point, approximately 200 ml would have passed into the collecting cylinder and no further flow determination was possible in the system employed. In one instance (Monkey 11) the urethral closure pressure was 62 cm of H_2O without stimulation of the detrusor. This animal was excluded from the study.

RESULTS

To determine the resistance to urinary flow under the experimental conditions, the pressures at which a flow of 2.5 ml per sec in dogs and 1.5 ml per sec in monkeys was observed were compared. These numbers were chosen arbitrarily. A somewhat higher flow was chosen in dogs, since the over-all flow rates at any given pressure would be higher in dogs than in monkeys. With this difference, the analysis is made at about the same pressure level in both dogs and monkeys.

Six monkeys did not have any flow through the urethra at 60 cm of H_2O, which was the maximum pressure that the system could generate; therefore they were assigned a value of 60 cm for the purpose of analysis. Table 1 shows the mean pressures and standard deviations in dogs. Table 2 lists the means of individual differences in pressure with standard deviations obtained by comparing measurements under the several stimulation conditions one with another. Tables 3 and 4 contain similar data for the 18 monkeys.

Effects of Stimulation

Since there were uncontrollable variables in the experiments, such as the size of the animal, each animal had to serve as its own control. This was achieved by comparing the pressures necessary to generate the chosen flows in unstimulated bladders (controls) with those in stimulated bladders. In monkeys the pressure required increased by an average of 16.4 cm of H_2O after stimulation (Table 4). This increase was significant ($P < 0.1$ by the one-sided t test).

TABLE 1. *Mean pressure required to produce urinary flow of 2.5 ml/sec in seven dogs*

	Mean Pressure	Standard Deviation	No. of Expt.
	cm of H_2O		
Control	39.0	8.25	7
Stimulation	42.4	7.82	7
Stimulation after succinylcholine	38.7	7.80	7
Stimulation after external sphincter fatigue	42.4	7.19	7

TABLE 2. *Pressures required to produce urinary flow of 2.5 ml/sec in seven dogs: Comparison of means of individual differences in pressures*

	Minus Control	Minus Stimulation	Minus Stimulation after Succinylcholine
Stimulation			
Pressure[a]	+3.4		
SD[b]	5.07		
No.[c]	7		
Stimulation after succinylcholine			
Pressure	−0.3	−3.7	
SD	3.61	6.47	
No.	7	7	
Stimulation after external sphincter fatigue			
Pressure	+3.4	0.0	+3.7
SD	7.17	4.63	7.76
No.	7	7	7

[a] In cm H_2O.
[b] Standard deviation on the individual differences.
[c] Number of experiments.

TABLE 3. *Mean pressure required to produce urinary flow of 1.5 ml/sec in 18 monkeys*

	Pressure	Standard Deviation	No. of Expt.
	cm of H_2O		
Control	33.9	7.79	18
Stimulation	50.3	10.46	18
Stimulation after succinylcholine	39.4	7.21	12
Stimulation after external sphincter fatigue	38.8	8.05	18

In dogs no such change was incurred by stimulation. Of the seven dogs five showed moderate increases in pressure, while two dogs had decreases in pressure during stimulation with 2 and 6 cm of H_2O, respectively (Dog 4714, paraplegic, and Dog 4804, normal bladder innervation). These two animals were exceptional in that they had markedly larger bladder volumes than the others, as well as hypertrophy of the prostate.

TABLE 4. *Pressures required to produce urinary flow of 1.5 ml/sec in 18 monkeys: Comparison of means of individual differences in pressure*

	Minus Control	Minus Stimulation	Minus Stimulation after Succinylcholine
Stimulation			
Pressure[a]	+16.4		
SD[b]	11.01		
No.[c]	18		
Stimulation after succinylcholine			
Pressure	+2.1	−11.6	
SD	6.21	7.72	
No.	12	12	
Stimulation after external sphincter fatigue			
Pressure	+4.9	−11.5	−0.3
SD	8.10	6.78	2.01
No.	18	18	12

[a] Pressure in cm of H_2O.
[b] Standard deviation on the individual difference.
[c] Number of experiments.

Effects of Succinylcholine

Using the same voltage for stimulation after administration of succinylcholine (15 to 25 mg per kg), no statistical differences could be established on the basis of the mean of the pressures required for 2.5 ml per sec flow and mean control pressures. Using the pressures required during stimulation without succinylcholine as a basis for comparison, no significant change was found in dogs. In monkeys, however, a decrease in pressure by an average of 11.6 cm of water was found. Using the one-sided t test, P was less than 0.1 for this difference.

This group contains only 12 monkeys since 5 in which pudendal neurectomy had been performed before succinylcholine administration were not included. In addition, technical considerations made it impractical to stimulate one monkey after succinylcholine administration.

Effect of Pudendal Neurectomy

In five monkeys in which pudendal neurectomy was performed, mean pressures and means of individual differences in pressure required to obtain 1.5 ml per sec flow are compared in Table 5. The change in pressure between control values and those obtained in stimulated bladders—a rise of 2 cm H_2O—was significant ($P < 0.1$ using the one-sided t test). The pressures required after administration of succinylcholine cannot be shown to differ from either control pressures or pressures required when stimulation was applied after pudendal neurectomy.

Effects of Electrical External Sphincter Fatigue

Hald et al. (17) suggested that fatigue by tetanic stimulation of the sphincteric region prior to bladder stimulation might produce a better urinary flow.

TABLE 5. *Mean pressure required to produce 1.5 ml/sec urinary flow and comparison of means of individual differences in pressure in 5 monkeys after pudendal neurectomy*

	Mean Values	Minus Control	Minus Stimulation after Succinylcholine
Control			
Pressure[a]	27.8		
SD[b]	3.06		
No.[c]	5		
Stimulation after succinylcholine			
Pressure	28.8	+1.0	
SD	3.54	2.35	
No.	5	5	
Stimulation			
Pressure	29.8	+2.0	+1.0
SD	3.66	1.23	3.00
No.	5	5	5

[a] Pressure in cm of H_2O.
[b] Standard deviation on means.
[c] Number of experiments.

This concept was explored in this study. Different placement of the electrodes, both in the retropubic space and perineally, was attempted with a variety of stimulus characteristics. In preliminary experiments on 10 monkeys using the Grass stimulator, the optimal placement for the electrodes was in the levator substance at the apex of the prostate, reached by a retropubic route. The optimal frequency was 200 to 250 pulses per second of approximately 1 msec duration. The voltages applied varied from 4 to 12.3 v. The tetanic current was maintained for 30 to 60 sec and was immediately followed by detrusor stimulation. The effect of the fatigue tapered off rapidly, disappearing within 20 min.

Tables 1 and 3 list the pressures required to generate the control flows—1.5 ml per sec in monkeys and 2.5 ml per sec in dogs—under optimal fatigue conditions. Figure 1 presents the same data graphically.

Again, in dogs no difference between mean control pressures, mean stimulation pressures, and mean stimulation pressures after succinylcholine could be demonstrated. In monkeys, similarly, no proof was found for the existence of a difference between the pressures after stimulation immediately preceded by fatigue and the pressures after stimulation following administration of Anectine or control pressures. As compared with stimulation alone (i.e., using no measures to counteract the increased resistance), however, stimulation after fatigue yielded a decrease in pressure of 11.6 cm H_2O on the average. This difference was significant ($P < 0.05$ by the one-sided t test).

Similar results can be found by comparing flows at a given pressure. The pressure for comparison of flows was arbitrarily defined as the pressure at which stimulation after fatigue yielded a flow of 1.5 ml per sec in monkeys and 2.5 ml per sec in dogs. The mean changes in flow and their standard

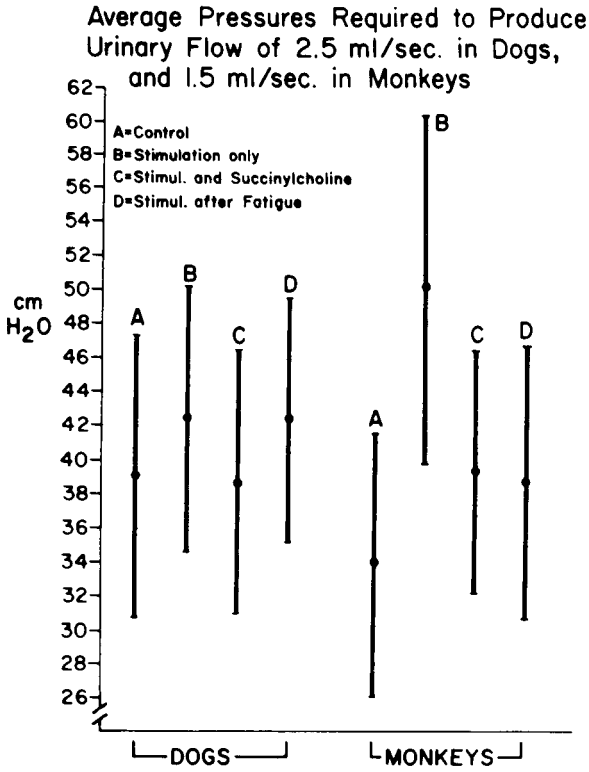

FIG. 1. Average pressures (±SD) required to produce urinary flow of 2.5 ml/sec in dogs and 1.5 ml/sec in monkeys.

deviations are listed in Tables 6 and 7 for dogs and monkeys, respectively. Again, in dogs equality among the mean values for the four experimental procedures could not be disproved ($P > 0.1$). In monkeys a difference could be shown between the effects of stimulation and those of the other three modalities ($P < 0.1$); equality of the means for the latter three modalities could not be disproved ($P > 0.1$).

DISCUSSION

Neurogenic bladder disturbances uniformly cause a decrease in urinary flow rates, but not necessarily in intravesical pressures (18). In the paraplegic a paradoxical action of the external sphincter—as an element of the general spasticity of the somatic muscles—seems to be present to a varying degree in nearly all cases of reflex emptying (19–22). During electrical stimulation this spasticity or paradoxical external sphincter action may be enhanced by: (i) increased afferent impulses through the pelvic plexus, the sympathetic chain or the pudendal nerve (23), (ii) excitation of efferent fibers in the pudendal nerve, or (iii) direct spread of current to the perineal muscles.

In the experiments presented here, in normal monkeys the increase in re-

TABLE 6. *Mean flows and comparison of means of individual differences at pressures required for urinary flow of 2.5 ml/sec in seven dogs after external sphincter fatigue*

	Mean Values	Minus Control	Minus Stimulation	Minus Stimulation after Succinylcholine
Control				
Flow[a]	3.4			
SD[b]	1.22			
No.[c]	7			
Stimulation				
Flow	2.8	−0.6		
SD	0.59	0.88		
No.	7	7		
Stimulation after succinylcholine				
Flow	3.2	−0.2	+0.4	
SD	0.93	1.02	0.69	
No.	7	7	7	
Stimulation after external sphincter fatigue				
Flow		−0.9	−0.3	−0.7
SD		1.22	0.59	0.93
No.		7	7	7

[a] Mean flow in ml/sec.
[b] Standard deviation from the mean.
[c] Number of experiments.

sistance to urinary flow during stimulation definitely can be ascribed to striated muscles since succinylcholine abolished this effect. Pudendal neurectomy reduced the changes markedly, but a small increase was still present, pointing to the possibility of direct current spread. The presumption that the increased resistance is due to striated muscle innervated by the pudendal nerve seems justified.

This observation correlates well with circumstantial clinical evidence. Thus most investigators find electrical bladder stimulation most suitable in lower motor neuron lesions such as spina bifida or cauda equina syndrome from other causes (11, 13, 15). That direct current spread may take place is suggested by the finding of Halverstadt and Leadbetter (11) that rearrangement of electrodes more cranially on the bladder in a female patient with a lower motor neuron lesion improved the effect of stimulation. A more direct item of evidence is the report of Hald et al. (15) on improved function of a stimulator in a paraplegic after pudendal nerve resection.

The difference in the increase in resistance to urinary flow during stimulation between dogs and monkeys shown in this study indicates that the monkey is a better model for experiments with detrusor stimulation than is the dog, probably because of differences in urethral anatomy. The dog, in contrast to the primate, has a long intrapelvic urethra which during micturition produces active peristalsis; in addition, the dog has no well defined external

TABLE 7. *Mean flows and comparison of means of individual differences required for urinary flow of 2.5 ml/sec in 18 monkeys after external sphincter fatigue*

	Mean Values	Minus Control	Minus Stimulation	Minus Stimulation after Succinylcholine
Control				
Flow[a]	2.1			
SD[b]	0.77			
No.[c]	18			
Stimulation				
Flow	0.3	−1.8		
SD	0.51	1.13		
No.	18	18		
Stimulation after succinylcholine				
Flow	1.5	−0.4	+1.1	
SD	0.56	0.71	0.68	
No.	12	12	12	
Stimulation after external sphincter fatigue				
Flow		−0.6	+1.2	0.0
SD		0.78	0.51	0.56
No.		18	18	12

[a] Mean flow in ml/sec.
[b] Standard deviation from the mean.
[c] Number of experiments.

sphincter (24). In spite of this, improvements in flow during electric detrusor stimulation after pudendal neurectomy in dogs have been achieved experimentally (25).

Several approaches have been proposed to mitigate the undesirable effect of bladder stimulation on the pudendal nerve. Creation of a lower motor neuron lesion in the paraplegic by intrathecal alcohol injections (24) or merely by pudendal neurectomy (25) has been suggested. Another possibility is the placement of electrodes in an arrangement that tends to minimize the amount of current reaction at the pudendal nerve (13, 26). The pulse wave form has also been found to influence the degree of pudendal involvement (26). Still another approach is the administration of urecholine. This increases the sensitivity of the bladder to stimulation, permitting a 30 per cent reduction in voltage (27) and with it a smaller outflow resistance (17).

In this paper a different approach is proposed. Tetanic stimulation fatigues the effector organ, i.e., the perineal muscles, so that their reactivity to stimulation is impaired for a few minutes. During that interval micturition can be induced at a lower sphincteric resistance. This method should be combined with efforts to limit the field of electrical current to the bladder wall itself, while directing as uniform a field as possible over the entire bladder (28).

On the basis of these experiments an implantable stimulator was devised. It consists of a passive receiver containing two independent circuits for reception and demodulation of two signals at different carrier frequencies and a

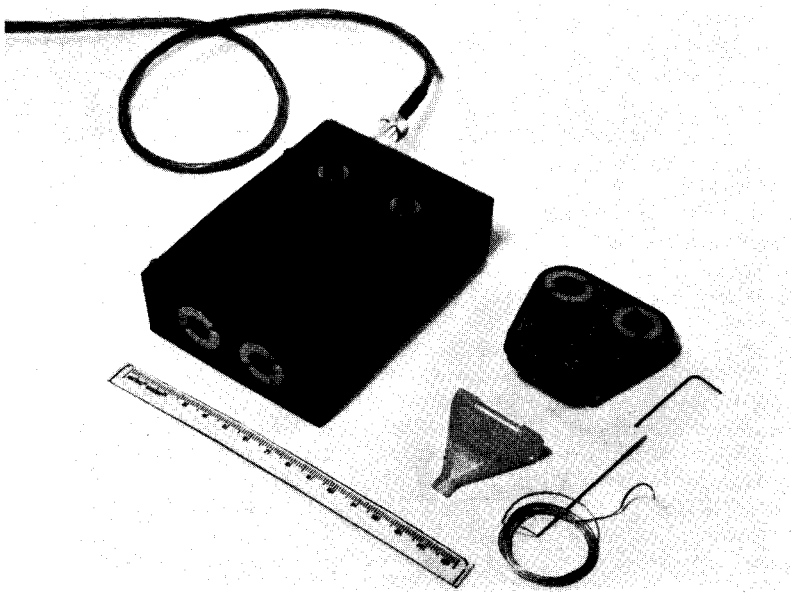

FIG. 2. Transmitter and implantable receiver. Six stainless steel Teflon coated electrodes are brought through the Silastic boot and secured after removal of the straight needle. Ruler is metric.

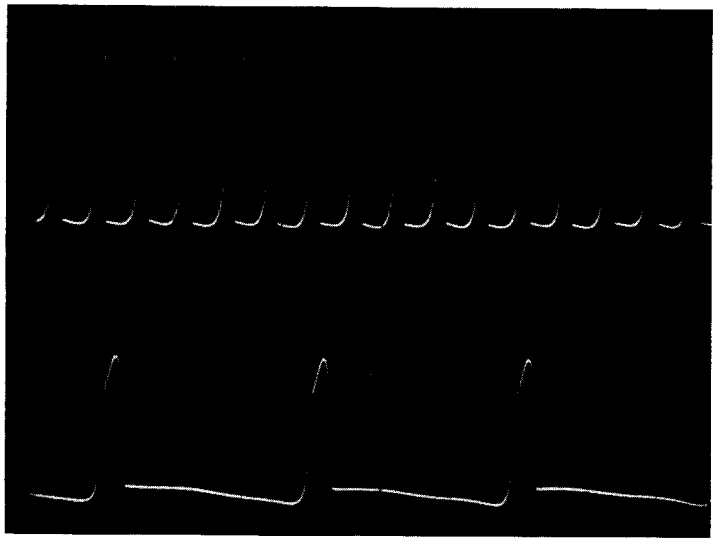

FIG. 3. Oscilloscope tracing of receiver output. Time: 10 msec per horizontal division. Voltage: 2 v per vertical division. *Upper tracing,* bladder stimulus; *lower tracing,* fatigue stimulus. Both channels were loaded with 300 ohm resistance and 2 microfarad capacitance in parallel.

transmitter. One channel of the receiver delivers high frequency fatigue stimulation to the sphincteric region and another supplies the bladder through four stainless steel electrodes. The transmitter is similarly divided into two sections with a common power source, the one designed for fatigue transmission

and the other for detrusor stimulation (Fig. 2). Figure 3 shows the pulse wave form with a load of 300 ohms in parallel with 2 microfarad capacitance.

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